REMARKS

Claims 1-16 were pending in the instant application. Claims 1-13 and 15-16 have been canceled. Claim 14 has been amended. New claims 17-42 have been added. Accordingly, claims 14 and 17-42 will be pending after entry of the instant amendment. Applicants reserve the right to prosecute the claims as originally filed in this or a continuing application.

Support for the claim amendments can be found throughout the claims and specification as originally filed. No new matter has been added. In particular, support for the claim amendments and new claims can be found in the specification as indicated in the table below.

Claim number	*Support*
Claim 14	Page 1, lines 10-13 and page 7, lines 6-13
Claims 17-18	Page 7, lines 12-13 and lines 29-30
Claims 19-23	Page 7, lines 6-13
Claim 24	Page 6, lines 6-7 and lines 21-25
Claim 25-27	Page 9, lines 3-10
Claims 28-31	Page 9, lines 8-13
Claims 32, 38 and 39	Page 12, lines 3-11
Claims 33-34	Page 7, lines 21-23
Claims 35-37	Page 9, lines 23-26
Claims 40-42	Page 20, lines 1-4, lines 23-26 and page 21, lines 13-14

Claim Rejections Under 35 USC § 102

Claim 14 is rejected as lacking novelty in view of Bielinska *et al.* (1996 *Nucleic Acids Research* 24(11):2176-2182). The Examiner relies on Bielinska *et al.* for teaching "a delivery mixture comprising a dendrimer capable of delivering a nucleic acid into cells (see page 2177, column 2 second paragraph)." Applicants respectfully traverse this rejection. The cited reference fails to teach each and every element of the present invention as recited in the claims amended herein.

Bielinska *et al.* is directed to a delivery mixture comprising a dendrimer capable of delivering a DNA molecule that ***mediates antisense inhibition*** of gene expression. In particular, Bielinska *et al.* report on the delivery of an ***antisense oligonucleotide*** (*e.g.*, a 27 base single-stranded DNA oligonucleotide) or an ***antisense expression plasmid*** (*e.g.*, a DNA plasmid expressing antisense mRNA) by forming a DNA-dendrimer complex, neither of which is useful in performing RNA interference ("RNAi").

Claim 14, as currently amended, is drawn to a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi. For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art must teach **each and every element** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Bielinska *et al.* fail to teach or suggest a delivery mixture comprising a dendrimer and a ***nucleic acid capable of mediating RNAi***. Indeed, Bielinska *et al.* fail to teach any nucleic acid molecule that ***mediates RNAi***. In view of the foregoing, Applicants respectfully request that the rejection of claim 14 under 35 § 102(a) be reconsidered and withdrawn.

Claim Rejections Under 35 USC § 103

Claim 14 is rejected under 35 U.S.C. §103(a) as being obvious over Yoo *et al.* (1999 *Pharm. Research* 16:1799-1804) in view of Hammond *et al.* (2001 *Nature* 2:110-119). The Examiner relies on Yoo *et al.* for teaching "a delivery mixture, comprising an antisense molecule and a dendrimer, capable of delivering an antisense molecule into cells (see bottom page 1799 to top page 1800)." The Examiner acknowledges that Yoo *et al.* fail to teach "a delivery mixture comprising a siRNA."

The Examiner further relies on Hammond *et al.* for teaching "two molecules used for silencing specific genes: antisense and dsRNA," and for further teaching that "of the two molecules used to administer to cells for silencing gene function, dsRNA is more potent and sequence specific than antisense." The Examiner concludes that "it would have been obvious to

one of ordinary skill in the art at the time the invention was made to use the delivery mixture comprising a dendrimer for delivering a dsRNA instead of an antisense molecule."

Applicants respectfully traverse. Reconsideration and withdrawal of the rejection in light of the following arguments is respectfully requested.

Claim 14, as currently amended, is drawn to a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNA interference (RNAi).

The instant invention relates to a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNA interference (RNAi). Applicants' disclosure teaches that RNAi is a "process whereby double-stranded RNA (dsRNA) induces ***the sequence-specific degradation of homologous mRNA*** in animals and plant cells." In contrast, Yoo *et al.* teach a delivery mixture comprising a dendrimer and an ***antisense molecule*** capable of delivering an antisense molecule into cells. In particular, Yoo *et al.* teach a dendrimer complexed with a phosphorothioate 2'-O-methyl antisense RNA oligonucleotide directed against the beta-globin 705 splice site (see page 1799, second column, last paragraph through page 1800, first column, first paragraph). The antisense RNA oligonucleotide is taught by Yoo *et al.* to correct splicing of a mutated intron in the beta-globin gene in a reporter assay (see page 1801, first column, second paragraph). Yoo *et al.* do not teach or suggest a delivery mixture comprising a dendrimer and a nucleic acid ***capable of mediating RNAi***, as presently claimed. Moreover, Yoo *et al.* teach that the delivery of antisense molecules with dendrimers overcomes a ***major hurdle in the antisense field*** of ***inefficient delivery*** of antisense olignonucleotides to their target sites (see page 1799, column 1, first paragraph). Nothing in the teachings of Yoo *et al.* suggests a need in the art for an ***alternate molecule to an antisense molecule*** for the ***silencing of gene expression***, let alone a nucleic acid molecule capable of mediating RNAi, *i.e.*, capable of mediating sequence-specific degradation of mRNA. Thus, based on the teachings of Yoo *et al.*, one would not be motivated to seek alternate molecules to antisense for gene silencing.

Hammond *et al.* disclose that specific genes can be silenced using "antisense methods, using either DNA or RNA," and, further, that "double-stranded (ds) RNAs have been shown to

inhibit gene expression in a sequence specific manner... [in] a biological process termed RNA interference." Hammond *et al.* do not teach or suggest a ***delivery mixture*** for delivering dsRNA to cells, let alone a delivery mixture comprising a ***dendrimer*** and a nucleic acid capable of mediating RNAi, as presently claimed. Moreover, nothing in the teachings of Hammond *et al.* suggests a need in the art for a delivery mixture for dsRNAs, let alone a delivery mixture comprising a dendrimer. Indeed, Hammond *et al.* teaches that "RNAi is being harnessed for reverse genetics in cultured Drosophila cells..." and that "***[t]his process is almost trivial because silencing can be achieved simply by adding the dsRNA to the culture medium***" (see page 117, paragraph bridging first and second columns). Thus, based on the teachings of Hammond *et al.*, one would not be motivated to make a delivery mixture for delivering RNAi-mediating nucleic acids.

Accordingly, one of ordinary skill in the art would not have been motivated to combine the teachings of the cited art to arrive at the present invention, as currently claimed, in view of the art at the time of filing. A case of *prima facie* obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The Examiner, however, has not established a *prima facie* case of obviousness as there is nothing in the teachings of Yoo *et al.* and Hammond *et al.* that would motivate one of ordinary skill in the art to combine the cited prior art references, let alone to combine them in such a way as to arrive at the claimed invention.

Moreover, even were the motivation to combine the teachings of the cited references to exist, (which it does not), the skilled artisan would have had no reasonable expectation of success in making such a combination. The skilled artisan would have readily understood, at the time the instant application was filed, that the results obtained for delivering an antisense molecule to cells by using a delivery mixture containing a dendrimer and an antisense molecule

(as taught by Yoo *et al.*) cannot be extrapolated to the delivery of a nucleic acid capable of mediating RNAi with any reasonable expectation of success because the molecules operate through very different cellular mechanisms. In particular, the state of the art at the time of filing recognized that an antisense oligonucleotide inhibits transcription and/or translation of target genes by base-pairing with the target sequence and blocking translocation of the transcription/translation machinery. In contrast, RNAi was recognized to involve the assembly of the RNA molecule with protein components to form a nuclease complex, RNAi-Inducing Silencing Complex (RISC), that RISC utilizes an active mechanism to search for the homologous mRNA target and ultimately mediates degradation of the mRNA target.

The Examiner appears to be applying an improper "obvious-to-try" standard in the instant case. However, this is not the standard required to establish obviousness under 35 U.S.C. §103. See *In re Dow Chemical Cp.,* 837 F.2d 469 (Fed. Cir.1988); see also *In re Eli Lilly & Co.,* F.2d 943 (Fed. Cir. 1990) ("A[n] 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure"). At best, the cited references might be viewed as providing such a suggestion, but falls far short of rendering obvious Applicants' claimed invention under 35 U.S.C. § 103. Given the distinct mechanism of RNAi as compared to that of antisense technology, the skilled artisan would not, based on the current state of the art and the teachings of Yoo *et al.* and Hammond *et al.*, have had any reasonable expectation of success in using a dendrimer to deliver a functional RNAi-mediating nucleic acid molecule. One skilled in the art would recognize that an antisense molecule and a nucleic acid capable of mediating RNAi cannot be used interchangeably because they operate through very different mechanisms, and thus the successful substitution of a nucleic acid molecule capable of mediating RNAi in the teachings of Yoo *et al.* is not predictable.

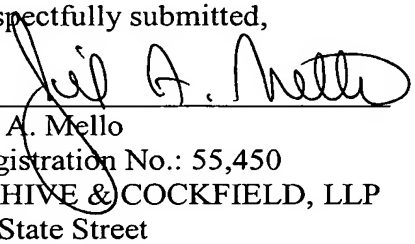
In summary, the Examiner has failed to point to any teaching in the Yoo *et al.* and Hammond *et al.* references that would compel one of ordinary skill in the art to make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they

should make the claimed composition or device, or carry out the claimed process" and ***[b]oth the suggestion*** and the ***reasonable expectation of success*** must be founded ***in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). In view of the foregoing, Applicants request that the rejection of claim 14 under § 103(a) be reconsidered and withdrawn.

In view of the above amendments and remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Dated: November 23, 2005

Respectfully submitted,

By 

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